Management of Bipolar II Disorder during Pregnancy and the Postpartum Period

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ABSTRACT

The spectrum of bipolar disorder (BPD) includes BP I, BP II, and BP not otherwise specified (NOS). The latter two conditions are thought to have a combined lifetime prevalence of 3.5% compared to a prevalence rate of 1.0% for BP I. Despite the combined high prevalence of BP II and BP NOS, surprisingly little is known about the course and treatment of these disorders during pregnancy and the postpartum period.

Brief hypomanic symptoms occur in the early puerperium in as many as 15% of women, and there is preliminary evidence that postpartum depression in some patients may be related to BP II or BP NOS. Yet there is paucity of data on the acute, and maintenance treatment of major depressive episodes during pregnancy in women with BP II and BP NOS. And there are no psychopharmacological studies on the acute or maintenance treatment of bipolar postpartum depression to guide clinical decision making. Also, there is a lack of screening instruments designed specifically for use before or after delivery in women with suspected bipolar disorder.

This paper reviews the current literature on the diagnosis, and treatment of BP II and BP NOS during pregnancy and in the postpartum period and makes recommendations for the detection and treatment of these disorders.

Introduction

Bipolar spectrum disorder includes bipolar I disorder (BP I), BP II, and BP not otherwise specified (NOS).[1] BP I is characterized by recurrent episodes of mania and depression while BP II is a depression preponderant illness with occasional episodes of hypomania. The illness course in BP NOS is also punctuated with manic and depressive symptoms but the disorder does not reach the DSM-IV threshold criteria for BP I or BP II. There is accumulating evidence that most of bipolarity exists beyond the realm of BP I. The U.S. National Comorbidity Survey Replication (NCS-R) published in 2007 reported lifetime prevalence estimates of 1.0% for BP I, 1.1% for BP II, and 2.4% for BP NOS.[2] Despite the combined high prevalence of BP II and BP NOS, surprisingly little is known about the course and treatment of these disorders during pregnancy and the postpartum period. The pharmacological treatment of BPD during pregnancy and breastfeeding poses major clinical and ethical dilemmas. The treating physician has to

carefully balance the need to minimize the impact of the illness for the mother, her unborn offspring, and her family against the potentially adverse fetal and neonatal effects of psychotropic drugs.[3] Another major challenge is that patients with BP II and BP NOS are often misdiagnosed as having major depressive disorder (MDD) resulting in inappropriate treatment. The NC S-R reported that only about 16% of patients with BP II and 8% of patients with BP NOS received appropriate medication compared with 25% for BP I. Similarly, the proportion of patients receiving no medication was quite high - 36% for BP I, 46% for BP II, and 68% for BP NOS.

Data on BPD during pregnancy are limited and contradictory. Pregnancy has traditionally been considered to have a positive effect on the course of BPD[4,5] with studies showing a reduced risk for psychiatric admission[6] and a lower risk for suicide.[7,8] Recent cohort studies have shown contrary results, however.[9,10] The possibility that the protective effect of pregnancy on the illness course could have been negated by the antidepressant led mood instability in these studies has to be considered. The postpartum period is generally considered a time of heightened vulnerability for recurrence of mood and psychotic episodes in the context of BPD.[9,11]

This brief review discusses the extant literature on the management of BP II and BP NOS during pregnancy and the postpartum period. Since there are no data on BP NOS in the peripartum period, the term BP II refers to both BP II and BP NOS in this article. A major aim of this paper is to raise awareness and stimulate research on the detection and appropriate treatment of these conditions. The risks associated with the use of the drugs during pregnancy and breastfeeding won't be described as these will be discussed in detail elsewhere in this issue.

Misdiagnosis of BP II as MDD

The misdiagnosis of BPD as MDD may not be uncommon in the postpartum period even though postpartum hypomania has been reported in 10-20% of women immediately after childbirth.[12-17] Results of a recent survey of 56 women referred for postpartum depression showed that the majority of patients

had a bipolar diathesis. The primary diagnoses of women in this study were as follows: MDD (46%), BP NOS (29%), BP II (23%), and BP I (2%).[18]

Hypomania, the distinguishing feature of BP II, is often missed leading to the under diagnosis and misdiagnosis of this disorder. Table 1 outlines clues to the bipolar diathesis of postpartum depression. BP II however, can be reliably diagnosed by expert questioning about symptoms of hypomania, usually in conjunction with collateral information from family and friends. The Mood Disorder Questionnaire is a simple self report screening instrument[1] but it may be biased toward the detection of BP I by requiring moderate/severe impairment for a positive screen for BPD.[19] According to the DSM definition, hypomania may not be severe enough to cause marked impairment; on the contrary, some individuals report enhanced functioning during hypomania.

Failure to diagnose hypomania frequently results in BPD being misdiagnosed as MDD and causes a delay in the initiation of appropriate treatment. The consequences of misdiagnosis can be particularly serious as treatment with antidepressants may precipitate mania or rapid cycling, and increase the risk for psychiatric hospitalization. The injudicious use of antidepressants in patients with a bipolar diathesis has also been linked to polypharmacy and treatment refractoriness.[20,21] Patients with BPD, particularly those with type II disorder, are at high risk for suicide attempts and completion. There is also a concern that antidepressants may cause mixed episodes that in turn may increase the risk for suicide.[22]

There are several reasons for the misdiagnosis of BP II as MDD. Hypomania after childbirth may be misconstrued as the normal joy related to the experience of motherhood. The DSM-IV does not acknowledge hypomania as a postpartum-onset specifier, which means that women with BP II are often misdiagnosed as having MDD in the postpartum period. Due to the general lack of awareness, clinicians may not inquire about episodes of mood elevation and unless asked specifically, women may fail to report hypomanic symptoms and focus instead on symptoms of depression. There are no screening instruments designed specifically for use before or after delivery in women with bipolar disorder. Commonly used screening instruments such as the Edinburgh Postnatal Depression Scale[23] and the Postpartum Depression Screening Scale[24] have not been validated in women with BPD.

Drug Treatment of BP II Depression during Pregnancy and Postpartum

Mood Stabilizers

There are no reports on the acute treatment of bipolar depression during pregnancy or postpartum. Data on the effectiveness of mood stabilizers in the maintenance treatment of BPD during pregnancy comes from studies of women who continued versus discontinued these medications. A prospective study of 89 pregnant women with BPD including 28 women with BP II reported that the overall recurrence rate was 71%.[9] Among women who discontinued versus continued mood stabilizers during pregnancy, the recurrence risk was twofold greater, and the median time to first recurrence was more than fourfold. Most recurrences were depressive or mixed (74%) and, 47% occurred during the first trimester. Recurrence latency was 11 times shorter after abrupt versus gradual discontinuation of mood stabilizer. Predictors of recurrence included a diagnosis of BP II, earlier onset, more recurrences/year, recent illness, use of antidepressants, and use of anticonvulsants versus lithium. Due to the concomitant use of medications such as antidepressants, neuroleptics, and benzodiazepines, it is difficult to discern the exact role of mood stabilizers in this study. Another prospective study compared the recurrence risks among 26 women with BPD (19 BP I, 6 BP II, 1BP NOS) who continued lamotrigine treatment to those who discontinued mood stabilizers during pregnancy.[25] The results of these two studies replicated the retrospective findings of a study showing high postpartum recurrence rates following the discontinuation of lithium during pregnancy.[26] An open-label trial found that divalproex was not significantly more effective than monitoring without drug for the prevention of postpartum episodes in women with BP I and BP II.[27]

Antidepressants

Data on the effectiveness and safety of antidepressants are lacking since patients with BPD are routinely excluded from studies on the use of antidepressants during pregnancy or after delivery. Women who are on antidepressants should be carefully watched for cycle acceleration or a mood switch to hypomania or mania. Antidepressants may also cause mixed symptoms such as agitation, irritability, racing of thoughts

and distractibility. Use of antidepressants during pregnancy, especially after discontinuation of mood stabilizers has also been linked to a higher risk of depressive recurrences.[9] Sharma reported three cases of early-onset postpartum depression in which bipolarity in the form of postpartum psychosis, mania and rapid cycling, manifested following antidepressant treatment. In all cases there was no past history of psychiatric disturbance but there was a family history of BPD.[28]

Neuroleptics

There is increasing usage of neuroleptics for the depressive and maintenance phase of BPD but there are limited data on their use in pregnancy. In one study placental passage, defined as the ratio of umbilical cord to maternal plasma concentrations, was highest for olanzapine followed by haloperidol, risperidone and quetiapine.[29] Due to reports of gestational diabetes women on atypical neuroleptics need to be monitored closely.[30-32] Exposure to atypical neuroleptics during pregnancy is also associated with increased infant birth weight and large for gestational age births.[33] A prospective cohort study of 25 women with BP I or BP II found that olanzapine used alone or in combination with an antidepressant or mood stabilizer, was associated with a lower risk of postpartum mood episodes (18% versus 57%) than treatment with mood stabilizers, antidepressants, or no medication for a minimum of four weeks post delivery.[34]

Acute and Maintenance Treatment of Bipolar Depression during Pregnancy

Even though hypomania may occasionally be associated with interpersonal, legal, and financial difficulties, the acute and maintenance treatment of depression is the main focus of treatment in individuals with BP II. Antidepressants should be avoided in women who require treatment for a recurrence of depression during pregnancy or the postpartum period.[28] In general, the treatment of breakthrough episodes of depression should follow the guidelines for bipolar II depression[35] with additional considerations as listed in Table 2. A trial of quetiapine, lamotrigine, or lithium should be considered in women who have depressive episodes but are not on any maintenance medication.

Treatment of Postpartum Bipolar Depression

The lack of pharmacological data on BP II depression is surprising given the high prevalence of hypomanic symptoms in the postpartum period, the unique treatment challenges posed by bipolar depression, and the heightened risk of suicide associated with bipolar spectrum disorder. Determination of whether postpartum depression is related to MDD or to BPD is crucial for appropriate treatment planning including implementation of strategies for risk assessment.

Given the prevalent nature of BPD and the potentially serious consequences of its misdiagnosis and inappropriate treatment, all women receiving antenatal care should be screened for BPD by inquiring about personal and family history of bipolar disorder. This will permit early identification of at risk women and application of formal risk assessment and management plan including close follow-up during the period of risk.[36] It may also provide an opportunity to address avoidable risk factors such as general levels of stress and sleep disruption in late pregnancy and early postpartum.[37,38]

Antidepressant monotherapy should be contraindicated. Patients on antidepressants in combination with mood stabilisers need to be monitored closely for impending signs of mood instability. Currently, no data exist on the use of lithium, anticonvulsants, or atypical neuroleptics in the acute treatment of bipolar depression in the postpartum period. For the acute treatment of bipolar II depression, quetiapine has been recommended as the first line option; and lithium, lamotrigine and divalproex as the second line options. For the maintenance treatment of bipolar II depression, both lithium and lamotrigine are considered as first line options and divalproex as the second line option. There are no data on the efficacy of quetiapine in the maintenance treatment.[34] Compatibility with breastfeeding is an important consideration in the choice of medication during the postpartum period. Other clinical factors to consider should include the rapidity of onset of action, the effect on sleep, and the role of the medication in the management of comorbid psychiatric disorders.

Conclusions

Treating women with BP II and BP NOS during pregnancy and postpartum can be challenging. There are no screening instruments designed specifically for use before or after delivery in women with suspected bipolarity and there is paucity of psychopharmacological data to guide clinical decision making in the acute or maintenance treatment of these disorders. Given the prevalent nature of bipolarity beyond BP I and the potentially serious consequences of its misdiagnosis and inappropriate treatment, all women receiving antenatal care should be screened for bipolar spectrum disorder. Clinicians have to carefully consider the reproductive safety data as well as the efficacy and general safety of medications before making a decision about the appropriate treatment intervention during pregnancy and postpartum.

APPENDIX

TABLE 1 Clues to Postpartum Bipolarity

- Postpartum hypomania
- Onset of depression immediately after delivery
- Atypical features (DSM-IV criteria), racing of thoughts, and concomitant psychotic symptoms
- Family history of bipolar disorder in a first degree relative
- Response to antidepressants [rapid response, loss of response, induction of hypo(mania) or depressive mixed episodes, and poor response]

TABLE 2 Maintenance and Prophylactic Treatment during Pregnancy - General Considerations

- Risks of medication to the fetus must be balanced against the risks of not treating the illness
- Avoid antidepressants, if possible
- For patients requiring medication during pregnancy, try using monotherapy at minimally effective doses
- Consider its effectiveness in the prophylaxis of postpartum mood episodes before selecting a drug to treat depression during pregnancy
- Benefits of breastfeeding should be balanced against the deleterious effect of sleep deprivation in triggering mood episodes
- Close monitoring of mood and sleep
- Target postpartum sleep disruption with adjunctive treatment

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